

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

PATENT SPECIFICATION

(11) 1 582 853

1 582 853

- (21) Application No. 25231/77 (22) Filed 16 June 1977
 (23) Complete Specification filed 19 May 1978
 (44) Complete Specification published 14 Jan. 1981
 (51) INT CL³ C07C 177/00; A61K 31/19, 31/045, 31/075, 31/215;
 C07C 35/06, 43/16//C07D 309/12; C07F 7/18

(52) Index at acceptance

C2C 1175 1672 200 215 220 225 227 22Y 231 237 240 248 253 259
 25Y 264 275 28X 294 295 304 313 31Y 338 348
 350 360 361 362 364 366 367 368 36Y 38Y 409 40Y
 43X 46Y 490 491 500 502 504 509 50Y 623 624 628
 643 644 652 658 65X 662 672 774 779 802 80Y AA
 BW TA WJ

(72) Inventors JEAN BOWLER

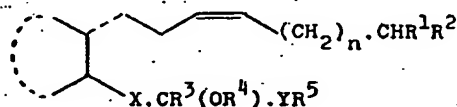


(54) PROSTANE DERIVATIVES

(71) We, IMPERIAL CHEMICAL INDUSTRIES LIMITED, Imperial Chemical House, Millbank, London SW1P 3JF, a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

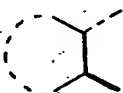
This invention relates to novel prostan derivatives, and in particular it relates to novel 4-prostene derivatives possessing high luteolytic activity. The new compounds are therefore useful as contraceptives or for control of the oestrous cycle in animals. The compounds may also be useful for the induction of labour or the early termination of pregnancy, or as hypotensives, for the relief of bronchospasm or the inhibition of gastric acid production.

According to the invention there is provided a prostan derivative of the formula:—

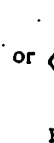


I

wherein either

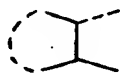


represents

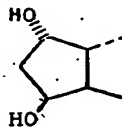


or

and R¹ is a carboxy radical, or a C₂₋₁₂ alkoxy carbonyl radical, or



represents



and R¹ is a hydroxymethyl or C₂₋₁₂ alkoxy methyl radical, R², R³ and R⁴, which may be the same or different, are each a hydrogen atom or a C₁₋₈ alkyl radical, X is an ethylene or *trans*-vinylene radical, Y is a C₁₋₈ alkyleneoxy radical, wherein the oxygen atom is bonded to R⁵, R⁵ is a phenyl or naphthyl radical which is unsubstituted or is substituted by one or more substituents selected from halogen atoms, nitro radicals and C₁₋₈ alkyl, alkoxy and halogenoalkyl radicals, and n is 1 to 4, and for those compounds wherein R¹ is a carboxy radical, the pharmaceutically or veterinarily acceptable salts thereof.

A suitable value for R^1 when it is a C_{2-12} alkoxycarbonyl radical is, for example, a methoxycarbonyl, ethoxycarbonyl, butoxycarbonyl or decyloxy-carbonyl radical, especially such a radical of 2 to 5 carbon atoms, and particularly a methoxycarbonyl radical; and a suitable value for R^1 when it is a C_{2-12} alkoxy-methyl radical is, for example, a methoxymethyl, ethoxymethyl, butoxymethyl or decyloxymethyl radical, especially such a radical of 2 to 5 carbon atoms.

A suitable value for any of R^2 , R^3 and R^4 when it is a C_{1-5} alkyl radical is, for example, a methyl, ethyl, propyl, butyl or pentyl radical, especially a methyl or ethyl radical and particularly a methyl radical.

n is preferably 1 or 2.

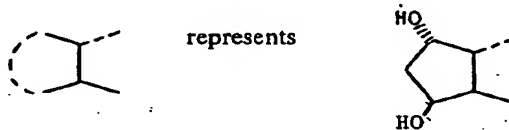
A suitable value for Y is, for example, a methylenoxy, ethylenoxy, trimethylenoxy, ethylideneoxy, isopropylideneoxy [$-\text{C}(\text{CH}_3)_2\text{O}-$], propylideneoxy, 1-methylpropylideneoxy [$-\text{C}(\text{CH}_3)(\text{C}_2\text{H}_5)\text{O}-$] or 1-ethylpropylideneoxy [$-\text{C}(\text{C}_2\text{H}_5)_2\text{O}-$] radical, particularly a methylenoxy or isopropylideneoxy radical.

A suitable halogen substituent in R^5 is, for example, a chlorine, fluorine, bromine or iodine atom, especially a chlorine atom; a suitable C_{1-5} alkyl or alkoxy substituent in R^6 is, for example, a methyl, ethyl, methoxy or ethoxy radical; and a suitable C_{1-5} halogenoalkyl substituent is, for example, a chloroalkyl or fluoroalkyl radical, such as a trifluoromethyl radical. Preferred values for R^5 contain not more than two substituents, and particular values are phenyl, chlorophenyl, especially 3-chlorophenyl, and trifluoromethylphenyl, especially 4-trifluoromethylphenyl, radicals.

A suitable pharmaceutically or veterinarily acceptable salt is, for example, an ammonium, alkylammonium containing 1 to 4 C_{1-5} alkyl radicals, alkanol-ammonium containing 1 to 3 2-hydroxyethyl radicals, or alkali metal salt, for example an ammonium, triethylammonium, ethanolammonium, diethanol-ammonium, sodium or potassium salt.

It will be observed that the novel prostane derivatives of the formula I contain at least three asymmetrically substituted carbon atoms, namely the two carbon atoms at which the side-chain are attached to the ring (the relative stereochemistry at these two positions is fixed in formula I) and the carbon atom of the group $-\text{CR}^5(\text{OR}^6)-$ in the lower side-chain. In addition, carbon atoms 2, 9 and 11 may also be asymmetrically substituted, so that it is clear that the compounds of the invention may exist in racemic or in optically active form. It is to be understood that the useful biological properties of a racemic compound, comprised of I and its mirror image, may be present to differing extents in the optical isomers, and that this invention relates to racemates and to any optically active form which shows the same useful properties, it being a matter of common general knowledge how the optically active forms may be obtained, and their biological properties determined. It is also to be understood that this invention relates to both C-15 epimers, that is, epimers at the $-\text{CR}^5(\text{OR}^6)-$ carbon atom in the lower side chain.

A preferred group of prostane derivatives of the invention having high luteolitic activity comprises compounds of the formula I wherein R^1 is a carboxy, methoxycarbonyl, ethoxycarbonyl, hydroxymethyl or methoxymethyl radical, R^2 , R^3 and R^4 , which may be the same or different, are each a hydrogen atom or a methyl radical,

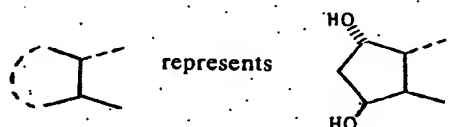


X is a *trans*-vinylene radical, Y is a methylenoxy or isopropylideneoxy radical, n is 1, and R^5 has the meaning stated above, particularly a phenyl radical, a halogenophenyl radical, for example a chlorophenyl radical, or a halogenoalkyl-phenyl radical, for example a trifluoromethylphenyl radical, and especially a phenyl, 3-chlorophenyl or 4-trifluoromethylphenyl radical. Preferred compounds in this group are methyl 16 - (4 - chlorophenoxy) - 19 α ,11 β ,15 α - trihydroxy - 17,18,19,20 - tetranor - 4 - *cis*,13 - *trans* - prostadienoate, 16 - (3 - chloro-phenoxy) - 9 α ,11 β ,15 α - trihydroxy - 17,18,19,20 - tetranor - 4 - *cis*,13 - *trans* -

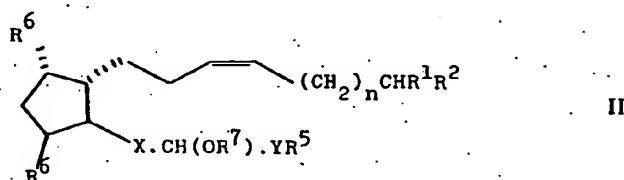
prostadienoic acid, and 16 - (3 - chlorophenoxy) - 17,18,19,20 - tetranor - 4 - *cis*,13-*trans* - prostadien - 1,9 α ,11 β ,15 α - tetraol.

The novel prostane derivatives of the invention may be manufactured by methods known in themselves for the manufacture of chemically analogous compounds. Thus, the following processes are provided as a further feature of the invention, wherein R¹, R², R³, R⁴, R⁵, n, X and Y have the meanings stated above, unless defined otherwise:—

(a) for those compounds wherein



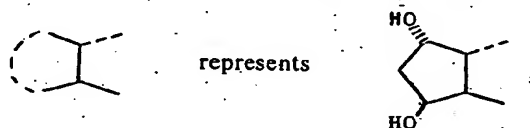
and R³ is a hydrogen atom, the hydrolysis, for example with an acid, such as acetic acid, of a compound of the formula:—



wherein R⁴ is a tetrahydropyran - 2 - yloxy radical and R⁷ is a tetrahydropyran - 2 - yl radical or a C₁₋₁₁ alkyl radical;

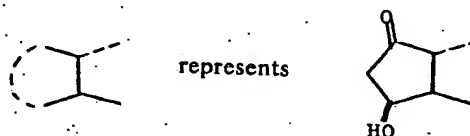
(b) for those compounds wherein R¹ is an alkoxycarbonyl radical, the reaction of the corresponding prostane derivative of the formula I wherein R¹ is a carboxy radical with a C₁₋₁₁ diazoalkane, or of a salt thereof with a C₁₋₁₁ alkyl halide, for example an alkyl iodide or alkyl bromide;

(c) for those compounds wherein R¹ is a hydroxymethyl radical and

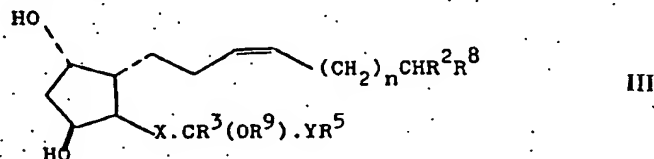


the reduction, for example with a complex metal hydride such as lithium aluminium hydride, of the corresponding prostane derivative of the formula I wherein R¹ is an alkoxycarbonyl radical;

(d) for those compounds wherein



and R³ is an alkyl radical, the oxidation, for example with chromium trioxide/pyridine complex, or Jones's reagent (chromic acid in acetone), of a compound of the formula:—



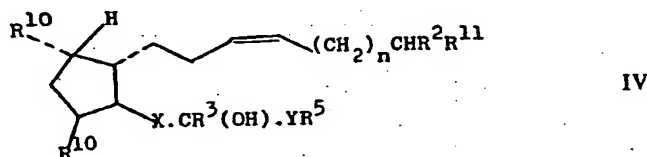
wherein R^3 is a C_{1-5} alkyl radical, R^6 is a C_{2-12} alkoxy carbonyl radical or a tri(C_{1-5} alkyl)silyloxy carbonyl radical, and R^9 is a C_{1-5} alkyl or tri(C_{1-5} alkyl)silyl radical, or a tetrahydropyran-2-yl radical, whereafter if necessary the protecting silyl or tetrahydropyran-2-yl groups are hydrolysed by treating the product so obtained with an acid;

(e) for those compounds wherein R^4 is an alkyl radical, the reaction of the corresponding prostane derivative of the formula I wherein R^4 is a hydrogen atom with an alkyl halide, for example an alkyl iodide, in the presence of one molecular proportion of a strong base, for example sodium hydride;

(f) for those compounds wherein

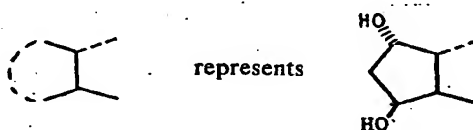


and R^3 is a C_{1-5} alkyl radical, the hydrolysis, with an acid, of a silyl derivative of the formula:—

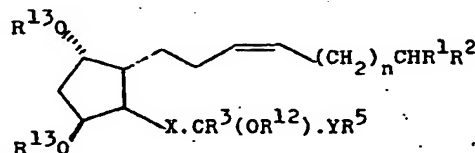


wherein R^{10} is a tri(C_{1-5} alkyl)silyloxy radical, R^3 is a C_{1-5} alkyl radical and R^{11} is a tri(C_{1-5} alkyl)silyloxy carbonyl, tri(C_{1-5} alkyl)silyloxymethyl, C_{2-12} alkoxy carbonyl or C_{2-12} alkoxy methyl radical;

(g) for those compounds wherein



R^1 is a carboxy or alkoxy carbonyl radical, and R^4 is a hydrogen atom, the hydrolysis with alkali of a compound of the formula:—

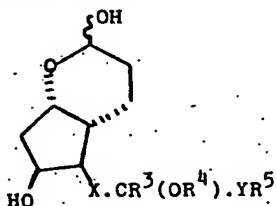


wherein R^2 , R^3 , R^5 , X and Y have the meanings given above, R^1 is a carboxy or a C_{2-12} alkoxy carbonyl radical, R^{12} is a hydrogen atom, when R^3 is an alkyl radical, or a carboxylic acyl radical such as an acetyl, benzoyl or *p*-phenylbenzoyl radical, when R^3 is a hydrogen atom, and R^{13} is a carboxylic acyl radical such as an acetyl, benzoyl or *p*-phenylbenzoyl radical;

(h) for those compounds wherein R^1 is a carboxy radical, and



the reaction of a lactol of the formula:—



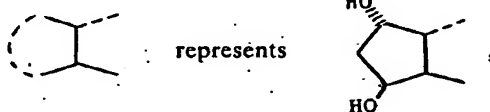
VI

with a triphenylphosphonium salt of the formula $\text{Ph}_3\text{P}^+(\text{CH}_2)_n\text{CHR}^2\text{COOH.Z}^-$ wherein Z^- is an anion, for example bromide, in the presence of a strong base.
 (i) for those compounds wherein R^1 is a carboxy radical, the hydrolysis of a corresponding compound of the formula I wherein R^1 is an alkoxycarbonyl radical.

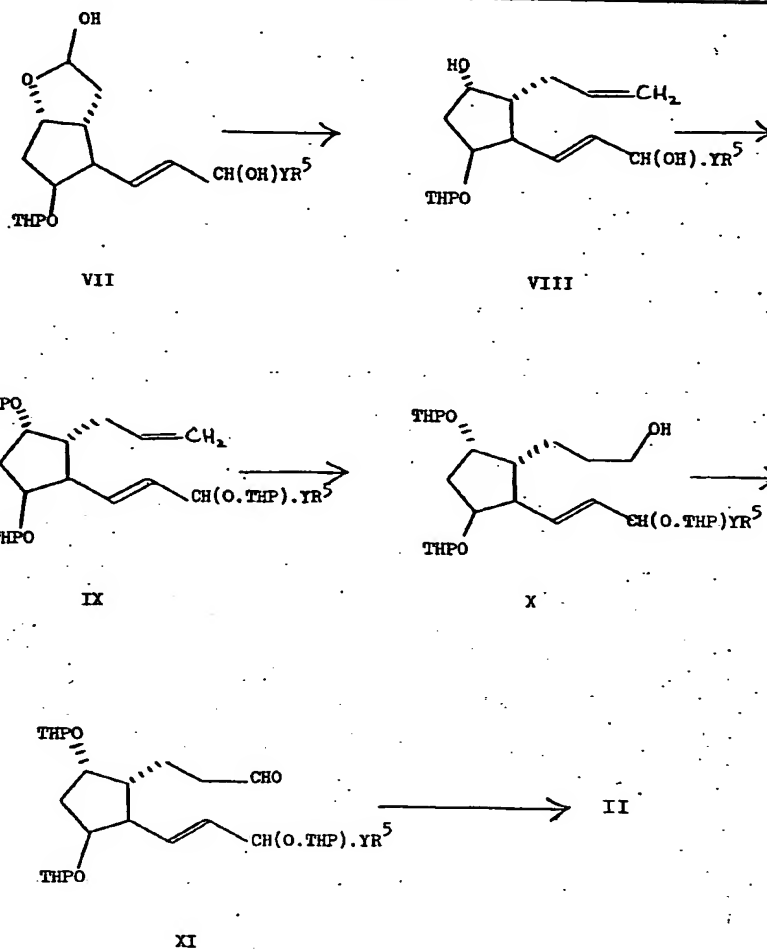
A starting material of the formula II may be obtained by reacting the known lactol VII with methyltriphenylphosphonium bromide in the presence of a strong base to give the allyl derivative VIII, which is treated with 2,3 - dihydropyran to give the tris(tetrahydropyran - 2 - yl) derivative IX. IX is reacted with borane in the presence of alkaline hydrogen peroxide to give the primary alcohol X, the primary alcohol X is oxidized with Collins' reagent to the aldehyde XI is subjected to a Wittig reaction with a triphenylphosphonium bromide derivative, $\text{Ph}_3\text{P}^+(\text{CH}_2)_n\text{CHR}^2\text{COOH.Br}^-$, in the presence of a strong base to give the required starting material of the formula II, wherein X is a *trans*-vinylene radical and R^2 is a tetrahydropyran - 2 - yl radical.

Starting materials of the formula II wherein X is an ethylene radical may be prepared by a sequence of reactions similar to that described above, but starting from the corresponding known saturated lactol in place of the unsaturated lactol VII.

The starting material of the formula III may be obtained by selective silylation of the corresponding prostan derivative of the invention wherein

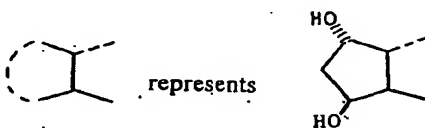


with, for example, $\text{tri}(\text{C}_{1-8}\text{alkyl})\text{silyl}$

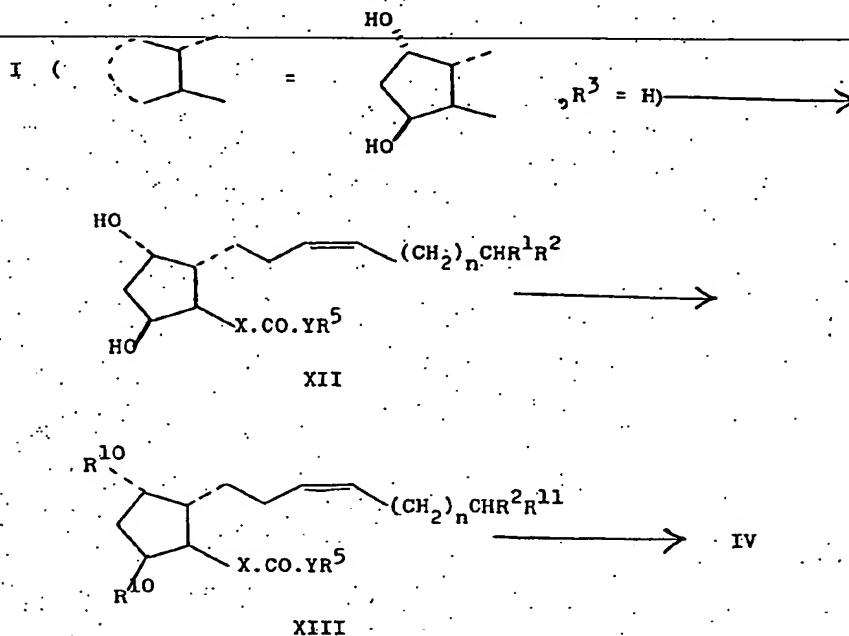


amide, such as diethylamino-dimethyl-t-butylsilane.

The starting material of the formula IV may be obtained from the corresponding compound of the formula I wherein

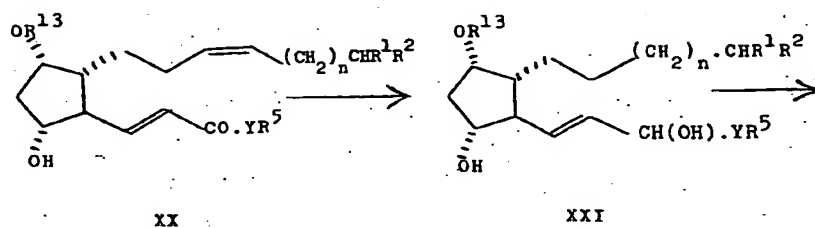
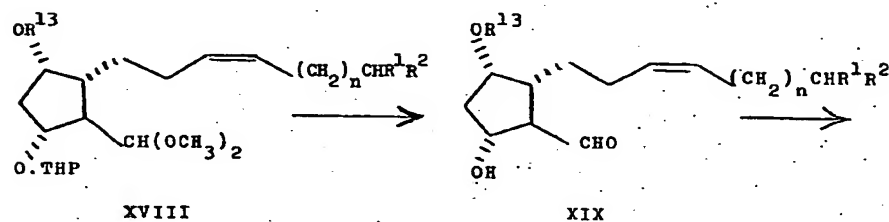
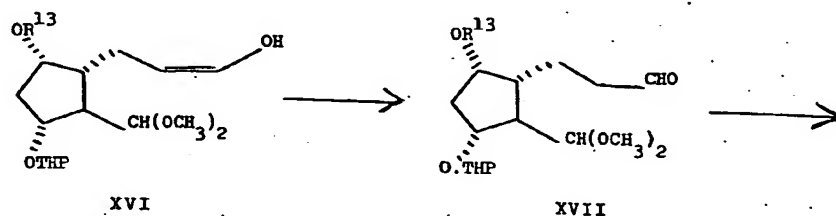
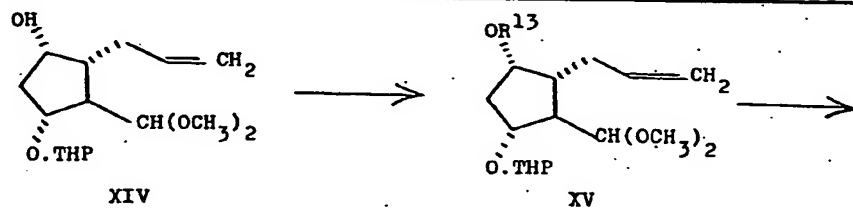


and R^3 is a hydrogen atom, by selective oxidation with one equivalent of Jones' reagent to give a ketone XII, which is treated with an excess of a silylating agent, for example a tri(C_{1-8} alkyl)silylamide, to protect the C-9 and C-11 hydroxy radicals, and the carboxy radical if present, giving the silyl derivative XIII. The silyl derivative XIII is then treated with a C_{1-8} alkylmagnesium halide to give the required starting material IV.



5 The starting material of the formula V may be obtained by treating the known
 5 acetal XIV with an acid chloride, R¹³Cl, in pyridine to give the protected acetal XV,
 which is reacted with borane and alkaline hydrogen peroxide to give the alcohol
 XVI. The alcohol XVI is oxidised to the aldehyde XVII with Collin's reagent, and
 10 the aldehyde XVII is reacted with a phosphonium salt, Ph₃P(CH₂)₂CHR¹R², in the
 presence of a base to give the olefin XVIII, which is hydrolysed selectively, for
 10 example with concentrated hydrochloric acid and 2% v/v of isopropanol in
 chloroform, to the hydroxy-aldehyde XIX. The hydroxy-aldehyde XIX is treated
 with a phosphonate reagent, (CH₃O)₂PO.CH₂CO.YR⁵, to give an enone XX, and
 15 the enone XX is reduced with a Meerwein-Ponndorf reagent to the diol XXI,
 which is epimerized by reaction with diethyl azodicarboxylate, triphenylphosphine
 and a carboxylic acid, R¹³OH, to a starting material V, (R¹² = R¹³ = carboxylic acyl,
 X = *trans*-vinylene). 15

Starting materials of the formula V wherein R³ is an alkyl radical may be
 obtained by reacting the enone XX with dihydropyran to give a tetrahydropyranyl
 ether or with a silylating agent to give a silyl ether XXII, which is treated with a
 20 Grignard reagent R³MgBr to give an enol XXIII, the protecting tetrahydropyranyl
 or trialkylsilyl group is hydrolysed, and the diol XXIV is epimerized in the reaction
 described above to give a starting material V (R¹² = hydrogen, R¹³ = carboxylic
 acyl, X = *trans*-vinylene). 20



5

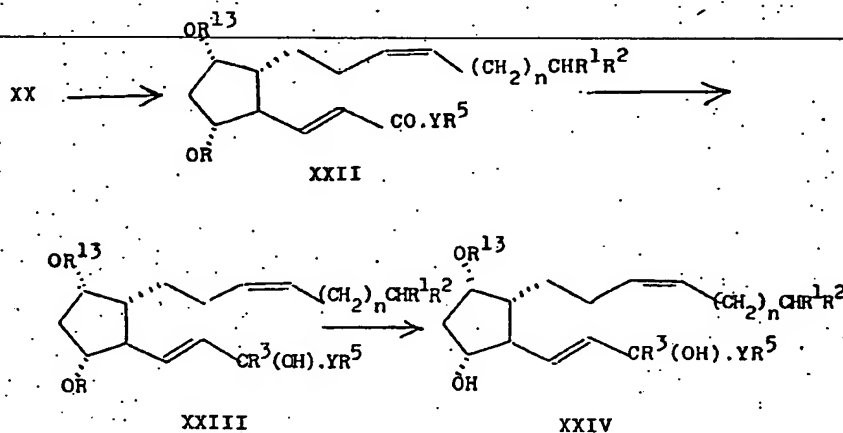
→ V ($R^{12} = R^{13} = \text{carboxylic acyl}$, X = *trans*-vinylene) THP = tetrahydropyran - 2 - yl

5

Corresponding starting materials V wherein X is an ethylene radical may be obtained in a completely analogous manner, but carrying out the reduction of the enone XX with sodium borohydride instead of with a Meerwein-Ponndorf reducing agent.

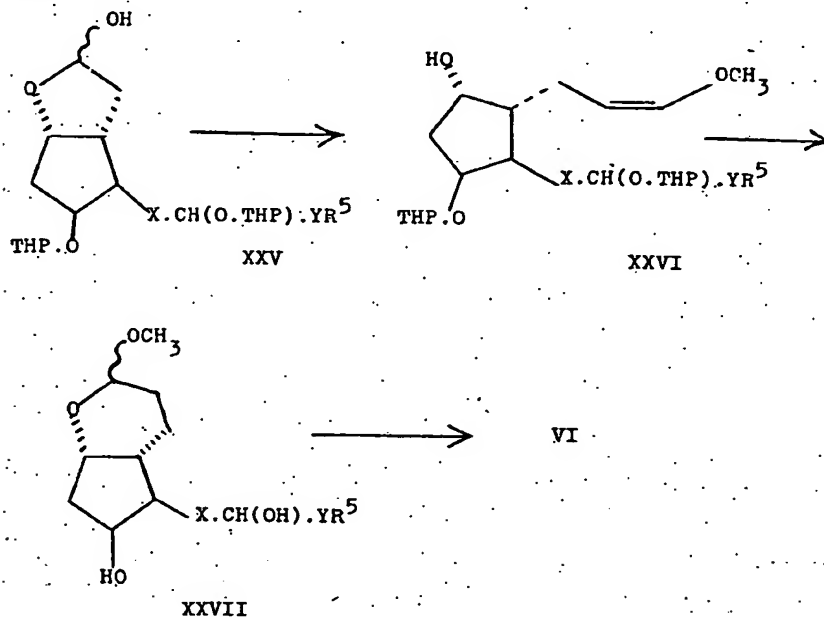
10

10



\rightarrow V ($R^{12} = H$, $R^{13} = \text{carboxylic acyl}$, $X = \text{trans-vinylene}$) $R = \text{tetrahydropyran-2-yl}$ or trialkylsilyl.

The starting material of the formula VI may be obtained from known bis(tetrahydropyranyl) derivatives XXV, by reaction thereof with a (methoxymethyl)triphenylphosphonium salt in the presence of a strong base to give an olefin XXVI, which on treatment at pH 2 with hydrochloric acid/potassium chloride buffer in methanol gives a compound XXVII. Further treatment of the compound XXVII at pH 1 with hydrochloric acid/potassium chloride buffer in tetrahydrofuran removes the protecting methyl group to give the required lactol starting material VI.



It is to be understood, of course, that an optically active prostane derivative of the invention may be obtained either by resolving the corresponding racemate, or by resolving a suitable starting material or other intermediate in the preparative reaction sequence.

As stated above, the prostane derivatives of the invention possess luteolytic properties, and in particular they are more active as luteolytic agents and less active as smooth muscle stimulants than the naturally occurring prostaglandins. Thus, for example, methyl 16 - (4 - chlorophenoxy) - 9 α ,11 β ,15 α - trihydroxy - 17,18,19,20 - tetranor - 4 - *cis*,13 - *trans* - prostadienoate is approximately 100 times as active as natural prostaglandin F₂ α as a luteolytic agent in hamsters (subcutaneous dosing) but possesses only approximately one twentieth of the smooth muscle stimulant activity.

When a prostane derivative of the invention is to be used for the induction of labour, it is used in the same way as it is known to use the naturally occurring prostaglandin E₂, that is by administering a sterile substantially aqueous solution containing from 0.01 to 10 μ g./ml., preferably 0.01 to 1 μ g./ml. of the compound, by intravenous infusion, or by transcervical extra-amniotic or intra-amniotic infusion until labour commences. Also, for this purpose, the prostane derivatives of the invention may be used in combination or concurrently, with a uterine stimulant, for example oxytocin, in the same way as it is known to use the natural prostaglandin in combination, or concurrently, with oxytocin for the induction of labour.

Certain of the compounds, including those wherein R¹ is a phydroxymethyl radical, are particularly effective when dosed orally. When a prostane derivative of the invention is to be used for control of the oestrus cycle in animals, for example cattle or horses, it is used in the same way as it is known to use the prostaglandin derivatives known as cloprostenol and fluprostenol for this purpose. The compounds may be used for this purpose in combination, or concurrently, with a gonadotrophin, for example pregnant mare serum gonadotrophin (PMSG) or human chorionic gonadotrophin (HCG) to hasten the onset of the next cycle.

Thus, according to a further feature of the invention there is provided a pharmaceutical or veterinary composition comprising a prostane derivative of the formula I together with a pharmaceutically or veterinarily acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, for example tablets or capsules, in a form suitable for inhalation, for example an aerosol or a solution suitable for spraying, in a form suitable for infusion, for example sterile, substantially aqueous, or oily, solutions or suspensions, or in the form of a suppository or pessary, suitable for anal or vaginal use.

The compositions of the invention may be prepared by conventional means, and may contain conventional excipients.

The composition is preferably in the form of a tablet, capsule or a substantially aqueous, sterile solution, and a particular preferred composition is a substantially aqueous, sterile solution containing from 25 to 150 μ g./ml., preferably from 25 to 75 μ g./ml.

The invention is illustrated, but not limited by the following Examples. Throughout the Examples, R_f values refer to silica gel plates supplied commercially by Merck (trademark) of Darmstadt, and the spots were visualised either by fluorescence under ultraviolet radiation, by exposure to iodine vapour, or by spraying the plates with a solution of ceric ammonium nitrate in sulphuric acid and heating. Organic solutions were dried with anhydrous magnesium sulphate.

Example 1.

To a solution of 16 - (3 - chlorophenoxy) - 9 α ,11 β ,15 α - tris(tetrahydropyran - 2 - yloxy) - 17,18,19,20 - tetranor - 4 - *cis*,13 - *trans* - prostadienoic acid (78 mg.) on dry methanol (1.2 ml.) was added toluene-*p*-sulphonic acid (116 μ l. of a 1% w/v solution in tetrahydrofuran) and the mixture was stirred at room temperature for 16 hours. Pyridine (3 drops) was added and the solvents were evaporated. The residue was extracted with diethyl ether (40 ml.) and washed successively with saturated sodium bicarbonate solution and brine. Evaporation of the solvent gave methyl 16 - (3 - chlorophenoxy) - 9 α ,11 β ,15 α - trihydroxy - 17,18,19,20 - tetranor - 4 - *cis*,13 - *trans* - prostadienoate. Purification by thin layer chromatography on silica gel plates using 3% v/v acetic acid in ethyl acetate as the developing solvent gave the pure compound, R_f=0.2. The n.m.r. spectrum in deuterated acetone showed the following characteristic bands (δ values):—

6.85—7.3, multiplet, 4 aromatic protons

5.1—6.05, multiplet, 4 aromatic protons

3.9-4.5, multiplet, 5H, —CH—O—

3.62, singlet, 3H, methyl ester.

The mass spectrum of the tris(trimethylsilyl) derivative showed $(\text{M—CH}_3)^+ = 639.2761$ (calculated for $\text{C}_{22}\text{H}_{32}\text{ClO}_6\text{Si}_3 = 639.2756$).

The tris(tetrahydropyranyl ether) used as starting material may be obtained as follows:—

Finely powdered methyluriphenylphosphonium bromide (536 mg.) was dried under vacuum for 1 hour and then dissolved in dimethyl sulphoxide (1.5 ml.), and the solution was cooled to room temperature. To this solution was added 0.625 ml. of a 2M solution of methanesulphonylmethyl sodium in dimethyl sulphoxide, followed by a solution of 4 β - [4 - (3 - chlorophenoxy) - 3 α - (tetrahydropyran - 2 - yloxy) - 1 - *trans* - butenyl] - 2,3,3a β , 6a β - tetrahydro - 2 - hydroxy - 5 β - (tetrahydropyran - 2 - yloxy)cyclopenteno[b] - furan (254 mg.) in a mixture of dimethyl sulphoxide (2.5 ml.) and toluene (1 ml.). The solution was stirred for 2 hours, and the solvent was evaporated under reduced pressure. The residue was shaken with water (1 ml.) and diethyl ether (5 ml.), and the aqueous phase was separated and re-extracted with diethyl ether (6 \times 2 ml.). The combined ether extracts were washed with saturated brine and dried, and the solvent was evaporated. The residue was chromatographed on silica gel (80 g.), and elution with 50% v/v ethyl acetate in toluene gave the allyl derivative, 2 α - allyl - 3 β - [4 - (3 - chlorophenoxy) - 3 α - (tetrahydropyran - 2 - yloxy) - 1 - *trans* - butenyl] - 4 β - (tetrahydropyran - 2 - yloxy)cyclopentan - 1 α - ol, $R_f = 0.5$ (50% v/v ethyl acetate in toluene).

To a solution of the allyl derivative (212 mg.) in methylene chloride (4.2 ml.) under an atmosphere of nitrogen was added successively redistilled 2,3-dihydropyran (192 μ l.) and a solution of anhydrous toluene - *p* - sulphonic acid in tetrahydrofuran (84 μ l. of a 1% w/v solution). After 10 minutes, pyridine (1 drop) was added, followed by ethyl acetate (20 ml.). The solution was washed successively with saturated sodium bicarbonate solution and brine, and was dried, and evaporation of the solvents gave the tris(tetrahydropyranyl ether), 2 α - allyl - 3 β - [4 - (3 - chlorophenoxy) - 3 α - (tetrahydropyran - 2 - yloxy) - 1 - *trans* - butenyl] - 1 α ,5 β - bis(tetrahydropyran - 2 - yloxy) - cyclopentane, $R_f = 0.6$ (25% v/v ethyl acetate in toluene).

To a solution of the tris(tetrahydropyranyl ether), (59 mg.), in dry tetrahydrofuran (2 ml.) under an atmosphere of argon at 0°C. was added 80 μ l. of a 1M solution of borane in tetrahydrofuran. After 3 hours, water (0.16 ml.), 1N sodium hydroxide (0.16 ml.) and 30% w/v hydrogen peroxide (0.4 ml.) were added successively, and the mixture was stirred at 0°C. for 30 minutes. The reaction mixture was diluted with water (10 ml.) and extracted with methylene chloride (4 \times 25 ml.). The organic extracts were washed successively with dilute sodium sulphite solution, sodium bicarbonate solution and brine, and were then dried, and the solvents were evaporated to give the primary alcohol, 3 - [2 β - [4 - (3 - chlorophenoxy) - 3 α - (tetrahydropyran - 2 - yloxy) - 1 - *trans* - butenyl] - 3 β ,5 α - bis(tetrahydropyran - 2 - yloxy)cyclopent - 1 α - yl]propanol, $R_f = 0.3$ (50% v/v ethyl acetate in toluene).

A solution of the primary alcohol (119 mg.) in methylene dichloride (2 ml.) was added to a stirred 0.5M solution of Collins' reagent (3.1 ml.). After 15 minutes at room temperature, the mixture was poured onto a column of "Florisil" (trade mark) magnesium silicate (14 g.), and eluted with 20% v/v ethyl acetate in methylene dichloride to give the aldehyde, 3 - [2 β - [4 - (3 - chlorophenoxy) - 3 α - (tetrahydropyran - 2 - yloxy) - 1 - *trans* - butenyl] - 3 β ,5 α - bis(tetrahydropyran - 2 - yloxy)cyclopent - 1 α - yl]propionaldehyde, $R_f = 0.6$ (50% v/v ethyl acetate in toluene).

Finely powdered (3 - carboxypropyl)triphenylphosphonium bromide (320 mg.) was heated to 100°C. under vacuum for 1 hour. The evacuated vessel was filled with an atmosphere of dry nitrogen, the solid was dissolved in dimethyl sulphoxide (3 ml.) and the solution was cooled to room temperature. To this solution was added 0.75 ml. of a 2M solution of methanesulphonylmethyl sodium in dimethyl sulphoxide, followed by a solution of the aldehyde described above (112 mg.) in a mixture of dimethyl sulphoxide (5 ml.) and toluene (2 ml.). The solution was stirred for 3 hours, and the solvent was evaporated under reduced pressure at a temperature below 40°C. The residue was shaken with water (2 ml.) and extracted with water (5 \times 10 ml.) and the extracts were discarded. The aqueous

solution was acidified to pH 3—4 with 2N aqueous oxalic acid, and extracted with a mixture of equal parts of ether and petroleum ether (b.p. 40—60°C., 5 x 6 ml.). The extracts were combined, washed with saturated brine and dried, and evaporation of the solvents gave the acid, 16 - (3 - chlorophenoxy) - 9 α ,11 β ,15 α - tris(tetrahydropyran - 2 - yloxy) - 17,18,19,20 - tetranor - 4 - *cis*,13 - *trans* - prostadienoic acid, $R_f = 0.5$ (50% v/v ethyl acetate in toluene).

Example 2.

To a solution of methyl 16 - (3 - chlorophenoxy) - 9 α ,11 β ,15 α - trihydroxy - 17,18,19,20 - tetranor - 4 - *cis*,13 - *trans* - prostadienoate (32 mg.) in diethyl ether (1 ml.) and tetrahydrofuran (1 ml.) was added lithium aluminium hydride (28 mg.). The mixture was stirred at room temperature for 10 minutes, the excess of hydride was destroyed by the addition of water (0.5 ml.), and the mixture was extracted with methylene chloride. The extracts were dried, and the solvent was evaporated to give 16 - (3 - chlorophenoxy) - 9 α ,11 β ,15 α - trihydroxy - 17,18,19,20 - tetranor - 4 - *cis*,13 - *trans* - prostadienol, $R_f = 0.3$ (5% v/v methanol in ethyl acetate).

The n.m.r. spectrum in deuterated acetone showed the following characteristic bands (δ values):—

6.8—7.4, broad multiplet, 4H, aromatic protons

5.3—6.05, broad multiplet, 4H, olefinic protons

3.2—4.5, broad multiplet, 7H, —CH—O— + 4 exchangeable protons.

The mass spectrum of the tetra(trimethylsilyl) derivative showed $M^+ = 698.3425$ (calculated for $C_{33}H_{53}ClO_4Si_4 = 697.29991$).

Example 3.

To a solution of methyl 16 - (3 - chlorophenoxy) - 9 α ,11 β ,15 α - trihydroxy - 17,18,19,20 - tetranor - 4 - *cis*,13 - *trans* - prostadienoate (12 mg.) on a mixture of methanol (1.37 ml.) and water (0.273) was added 0.273 ml. of a 1M solution of potassium hydroxide in methanol. The mixture was stirred at room temperature for 18 hours, acidified to pH 4.5 with aqueous oxalic acid, and diluted with ethyl acetate (40 ml.) The mixture was washed with brine, the organic phase was separated, dried, and the solvent was evaporated to give 16 - (3 - chlorophenoxy) - 9 α ,11 β ,15 α - trihydroxy - 17,18,19,20 - tetranor - 4 - *cis*,13 - *trans* - prostadienoic acid, $R_f = 0.3$ (5% v/v acetic acid in ethyl acetate). The n.m.r. spectrum in deuterated acetone showed the following characteristic bands (δ values):—

6.85—7.3, broad multiplet, 4H, aromatic protons

5.2—6.0, broad multiplet, 4H, olefinic protons

3.9—4.5, broad multiplet, 5H, —CH—O— + 4-exchangeable protons.

The mass spectrum of the tris(trimethylsilyl) derivative showed ($M\text{—CH}_3$) $^+ = 697.29966$ (calculated for $C_{33}H_{53}ClO_4Si_4 = 697.29991$).

Example 4.

16 - (3 - Chlorophenoxy) - 9 α ,11 β ,15 α - trihydroxy - 17,18,19,20 - tetranor - 4 - *cis*,13 - *trans* - prostadienoic acid

% w/v

0.003

Sodium phosphate B.P.

2.90

Sodium acid phosphate B.P.

0.30

Water for injection

to 100

The sodium phosphate B.P. was dissolved in about 80% of water, followed by the prostadienoic acid derivative, and when dissolved, the sodium acid phosphate

B.P. The solution was made up to volume with water for injection, and the pH was checked to be between 6.7 and 7.7. The solution was filtered to remove particulate matter, sterilised by filtration, and filled into pre-sterilised neutral glass ampoules under aseptic conditions.

The prostadienoic acid derivative may, of course, be replaced by an equivalent amount of another prostane derivative of the invention.

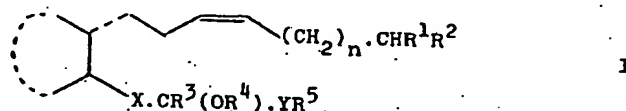
Example 5.

The process described in Example 4 was repeated, omitting the sodium phosphate B.P. and sodium acid phosphate B.P., to give ampoules containing a sterile aqueous solution of 16 - (3 - chlorophenoxy) - 9 α ,11 β ,15 α - trihydroxy - 17,18,19,20 - pentanor - 4 - *cis*,13 - *trans* - prostadienoic acid, which are used in the manner described in Example 4.

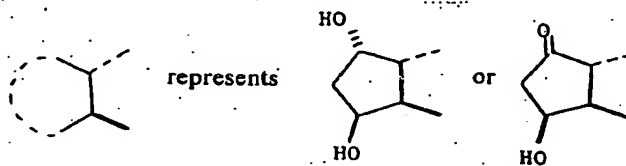
The prostadienoic acid derivative may be replaced by an equivalent amount of another prostanoic acid derivative of the invention, the give other sterile solutions.

WHAT WE CLAIM IS—

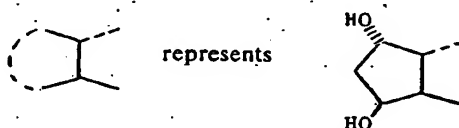
1. A prostane derivative of the formula:—



wherein either



and R¹ is a carboxy radical, or a C₂₋₁₂ alkyloxycarbonyl radical, or



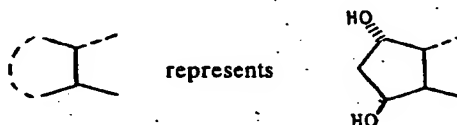
and R¹ is a hydroxymethyl or C₂₋₁₂ alkoxyethyl radical, R², R³ and R⁴, which may be the same or different, are each a hydrogen atom or a C₁₋₈ alkyl radical, X is an ethylene or *trans*-vinylene radical, Y is a C₁₋₈ alkyleneoxy radical, wherein the oxygen atom is bonded to R⁵, R⁵ is a phenyl or naphthyl radical which is unsubstituted or is substituted by one or more substituents selected from halogen atoms, nitro radicals and C₁₋₈ alkyl, alkoxy and halogenoalkyl radicals, and n is 1 to 4, and for those compounds wherein R¹ is a carboxy radical, the pharmaceutically or veterinarily acceptable salts thereof.

2. A prostane derivative as claimed in claim 1 wherein R¹ is a carboxy, hydroxymethyl, methoxycarbonyl, ethoxycarbonyl, butoxycarbonyl, decyloxycarbonyl, methoxymethyl, ethoxymethyl, butoxymethyl or decyloxymethyl radical, R², R³ and R⁴ are each a hydrogen atom or a methyl, ethyl, propyl, butyl or pentyl radical, n is 1 or 2, X has the meaning stated in claim 1, Y is a methyleneoxy, ethyleneoxy, trimethyleneoxy, ethylideneoxy, isopropylideneoxy, propylideneoxy, 1-methylpropylideneoxy or 1-ethylpropylideneoxy radical, and R⁵ is a phenyl or naphthyl radical which is unsubstituted or is substituted by one or more substituents selected from chlorine, bromine, iodine and fluorine atoms, a methyl, ethyl, methoxy, ethoxy, chloroalkyl and fluoroalkyl radicals, and for those compounds wherein R¹ is a carboxy radical, the ammonium, alkylammonium containing 1 to 4 C₁₋₈ alkyl radicals, alkanolammonium containing 1 to 3 2-hydroxyethyl radicals and alkali metal salts thereof.

3. A prostane derivative as claimed in claim 1 or 2 wherein R^1 is a carboxy, hydroxymethyl or methoxycarbonyl radical, R^2 , R^3 and R^4 are each a hydrogen atom or a methyl radical, X has the meaning stated in claim 1, n is 1 or 2, Y is a methyleneoxy or isopropylideneoxy radical, and R^5 is a phenyl or a chlorophenyl or trifluoromethylphenyl radical containing not more than two substituents.

4. A prostane derivative as claimed in claim 3 wherein R^5 is a 3-chlorophenyl or 4-trifluoromethylphenyl radical.

5. A prostane derivative as claimed in claim 1 wherein R^1 is a carboxy, methoxycarbonyl, ethoxycarbonyl, hydroxymethyl or methoxymethyl radical, R^2 , R^3 and R^4 , which may be the same or different, are each a hydrogen atom or a methyl radical,



X is a *trans*-vinylene radical, Y is a methyleneoxy or isopropylideneoxy radical, n is 1, and R^5 is a phenyl, 3-chlorophenyl or 4-trifluoromethylphenyl radical.

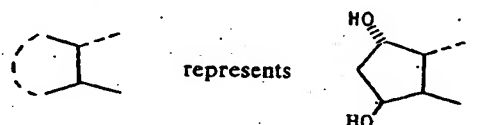
6. A prostane derivative as claimed in claim 1 which is methyl 16 - (4 - chlorophenoxy) - 9 α ,11 β ,15 α - trihydroxy - 17,18,19,20 - tetranor - 4 - *cis*,13 - *trans* - prostadienoate, 16 - (3 - chlorophenoxy) - 9 α ,11 β ,15 α - trihydroxy - 17,18,19,20 - tetranor - 4 - *cis*,13 - *trans* - prostadienoic acid, or 16 - (3 - chlorophenoxy) - 17,18,19,20 - tetranor - 4 - *cis*,13 *trans* - prostadien - 1,9 α ,11 β ,15 α - tetraol.

7. A prostane derivative as claimed in any one of claims 1 to 6 which is in racemic form.

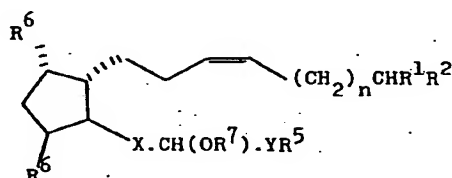
8. A prostane derivative as claimed in any one of claims 1 to 6 which is in an optically active and luteolytically effective form.

9. A process for the manufacture of a prostane derivative as claimed in claim 1 which comprises:—

(a) for those compounds wherein



and R^3 is a hydrogen atom, the hydrolysis of a compound of the formula:—

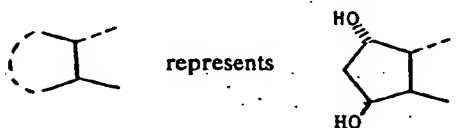


II

wherein R^5 is a tetrahydropyran - 2 - yloxy radical and R^7 is a tetrahydropyran - 2 - yl radical or a C_{1-8} alkyl radical;

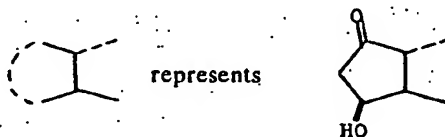
(b) for those compounds wherein R^1 is an alkoxy carbonyl radical, the reaction of the corresponding prostane derivative of the formula I wherein R^1 is a carboxy radical with a C_{1-11} diazoalkane, or of a salt thereof with a C_{1-11} alkyl halide;

(c) for those compounds wherein R^1 is a hydroxymethyl radical and



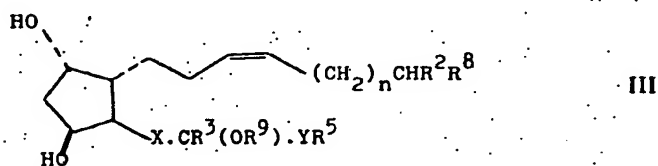
the reduction of the corresponding prostane derivative of the formula I wherein R^1 is an alkoxy-carbonyl radical;

(d) for those compounds wherein



5 and R^2 is an alkyl radical, the oxidation of a compound of the formula:—

5



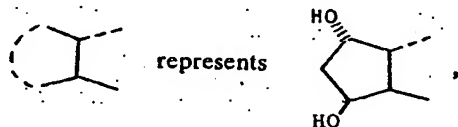
10 wherein R^3 is a C_{1-8} alkyl radical, R^8 is a C_{2-12} alkoxy-carbonyl radical or a tri(C_{1-8} alkyl)silyloxy-carbonyl radical, and R^9 is a C_{1-8} alkyl or tri(C_{1-8} alkyl)silyl radical, or a tetrahydropyran-2-yl radical, whereafter if necessary the protecting silyl or tetrahydropyran-2-yl groups are hydrolysed by treating the product so obtained with an acid;

10

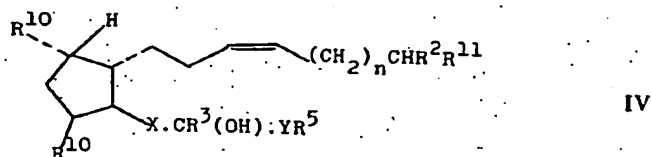
(e) for those compounds wherein R^4 is an alkyl radical, the reaction of the corresponding prostane derivative of the formula I wherein R^4 is a hydrogen atom with an alkyl halide in the presence of one molecular proportion of a strong base;

15 (f) for those compounds wherein

15



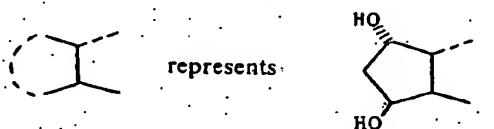
and R^3 is a C_{1-8} alkyl radical, the hydrolysis, with an acid, of a silyl derivative of the formula:—



20 wherein R^{10} is a tri(C_{1-8} alkyl)silyloxy radical, R^3 is a C_{1-8} alkyl radical and R^{11} is a tri(C_{1-8} alkyl)silyloxy-carbonyl, tri(C_{1-8} alkyl)silyloxymethyl, C_{2-12} alkoxy-carbonyl or C_{2-12} alkoxy-methyl radical;

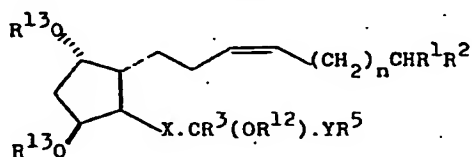
20

(g) for those compounds wherein



25 R^1 is a carboxy or alkoxy-carbonyl radical, and R^4 is a hydrogen atom, the hydrolysis with alkali of a compound of the formula:—

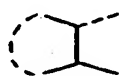
25



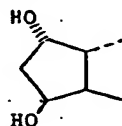
V

wherein R^1 is a carboxy or a C_{2-12} alkoxycarbonyl radical, R^{12} is a hydrogen atom, when R^3 is an alkyl radical, or a carboxylic acyl radical when R^3 is a hydrogen atom, and R^{13} is a carboxylic acyl radical;

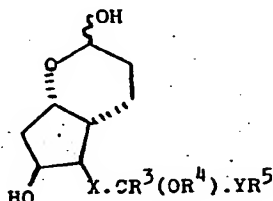
(h) for those compounds wherein R^1 is a carboxy radical, and



represents



the reaction of a lactol of the formula:—



VI

with a triphenylphosphonium salt of the formula $Ph_3P^+(CH_2)_nCHR^2COOH.Z^-$, wherein Z^- is an anion in the presence of a strong base; or (i) for those compounds wherein R^1 is a carboxy radical, the hydrolysis of a corresponding compound of the formula I wherein R^1 is an alkoxycarbonyl radical; and wherein R^1 , R^2 , R^3 , R^4 , R^5 , n , X and Y , unless otherwise defined, have the meanings stated in claim 1.

10. A pharmaceutical or veterinary composition comprising a prostane derivative as claimed in claim 1 together with a pharmaceutically or veterinarily acceptable diluent or carrier.

11. A prostane derivative as claimed in claim 1 substantially as hereinbefore described in any one of Examples 1 to 3.

12. A process as claimed in claim 9 substantially as hereinbefore described in any one of Examples 1 to 3.

13. A pharmaceutical or veterinary composition as claimed in Claim 10 substantially as hereinbefore described in Example 4. or 5.

J. D. ATKINSON
Agent for the Applicants.